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What can systems pharmacology contribute to drug development? Disease modelling as a predictive tool

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The paper "The Apoe-/- Mouse PhysioLab® Platform: A Validated Physiologically-based Mathematical Model of Atherosclerotic Plaque Progression in the Apoe-/- Mouse" by Jason Chan and colleagues [1] published in *BioDiscovery* 2012; 3: 2 is significant for several reasons. The pharmaceutical and biotechnology industries have become quite proficient at rational drug *design*, but rational drug *development* has not progressed as quickly (and development costs represent at least 70% of the billion dollar cost of taking a new chemical entity from conception to market). The reasons are clear: with the possible exception of antiinfectives, drugs for most therapeutic indications involve perturbations of complex interactive systems, our preclinical models all involve sweeping simplifications, and clinical trials usually involve heterogeneous groups of patients. Systems pharmacology approaches present one approach to addressing this complexity. Genetically engineered animal models offer useful approximations to human disease, but an animal model supplemented by a computational disease model greatly increases the range of questions that can be asked. Atherosclerosis presents a case in point: its aetiology is complex, it is affected by environmental and behavioural factors, including diet and smoking, and it may take several decades for the condition to progress to clinical disease. The Apoe-/- mouse reflects many of the features of human atherosclerosis, but there are important differences: in humans the dominant circulating atherogenic particles consist of LDL, while in the Apoe-/- mouse VLDL and IDL predominate. How do these differences affect the ability of the mouse model to predict the outcome of drug treatment or lifestyle changes in humans? Another limitation of the mouse model is that, despite its biological similarities with human atherosclerosis, it does not lead to the same clinical outcomes of angina and heart attack. Why is that? Given these limitations of the mouse model, can it still guide the development of prevention and treatment regimens to reduce the incidence of human heart disease? Chan et al have presented a computational model of atherosclerotic progression that has the potential to improve the predictive power of animal models of the disease, and (when the model is extended from mice to humans) to enable *in silico* clinical trials.

The Chan et al. model, based upon the Apoe-/- mouse, includes elements of cholesterol and macrophage trafficking, inflammation, oxidative stress, endothelial function, and thrombosis. It has the ability to predict relationships between biomarker data, pharmacodynamic effects and clinical outcomes. The model is the outcome of a collaboration between Entelos, an *in silico* modelling and simulation company, and Philip Morris, a tobacco company. A primary motive for developing the model appears to have been a desire to explore the relationship between smoking (and smoking cessation) and heart disease. However, the scope of the model is broad enough to enable it to be used

to model the effects of other lifestyle factors, including diet, and of drug treatment. As an example of drug effects, the model is used to predict effects of ezetimibe (which blocks cholesterol absorption from the intestine) on atherosclerotic progression. By publishing the model in *Biodiscovery*, the authors have agreed to make it available, free of charge, to all researchers.

In the past, drug developers have regarded computational models of complex biological systems with great scepticism. There has been an impression that the systems involved are so complex that any attempt to describe them mathematically must involve simplifying assumptions that were likely to undermine the dynamics of the system being modelled. There was pessimism about the ability to validate such large models (the Chan et al. model contains 94 ordinary differential equations, 524 algebraic equations, and 3,508 parameters). Yet these same drug developers have for eighty years relied heavily upon pharmacokinetic (PK) models in making drug development decisions, and PK models make equally sweeping simplifications. Why the difference? Two reasons: the first is that PK is a generic technology. We can use the same analytical methods to measure plasma levels of an antihypertensive as we use for an antidepressant, whereas the biological or pharmacodynamic (PD) endpoints that we use in disease modelling are different for every therapeutic area and for every drug class. Secondly, the mathematics of disease modelling and PD modelling is more complex. Both these factors still present barriers to wider use of disease modelling, but the barriers are yielding to advances in technology. Development of prognostic and pharmacodynamic biomarkers (and to an increasing extent, whole-body imaging techniques) is making it easier to collect the data required to validate complex models. In a recent review [2] I discussed the use of PD models of biomarker data in oncology. At present, regulatory approval of anticancer drugs requires clinical endpoints, which for slowly-progressing tumours means drug development times often in excess of ten years. Demonstrating and validating the predictive power of PD biomarkers in the context of computational disease models has the potential to revolutionise clinical drug development.

In recent years, computational disease models have been published covering a wide range of therapeutic areas. In HIV disease, we are presented with a complex interactive system where the immune system attacks the virus, and the virus attacks the immune system. Predicting PD effects of antiviral drugs requires a model that captures these complexities. Because of the very high mutation rates of retroviruses, in the early days of anti-retroviral drug development there was pessimism about whether sustained responses could be achieved in the face of acquired drug resistance. A disease model predicted, correctly, that with the use of multi-drug combinations, and with sufficient treatment intensity, disease progression could be arrested for many years [3]. In oncology, models of the cancer cell cycle [4] and three-dimensional virtual tumours have been used to predict optimal drug combination schedules [5]. Disease models have been described for diabetes, rheumatoid arthritis, hypertension and skin ageing [6].

These disease modelling approaches, formerly the province of theoreticians, are beginning to interest the wider drug development community. Quintiles, a major clinical research organization, recently published an extensive report on modelling and simulation practice throughout the drug development process [7]. In this report they note the increasing acceptance by the US Food and Drug Administration (FDA) of modelling and simulation studies in support of applications for marketing approval. As an example, they cite the FDA's Office of Clinical Pharmacology recommending concentration-QT modelling as a means of evaluating drug potential for QT interval disturbance [8]. Models such as that of Chan et al. are advancing the technology of computational disease modelling. In the long term, they should make possible higher success rates in clinical development, design of rational combination therapies, and tailoring of clinical protocols to individual patients. This is an ambitious agenda, but this paper represents a step in the right direction.

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